BOLD Connectivity Dynamics and its relationship to On-going Cognition

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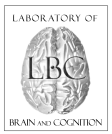
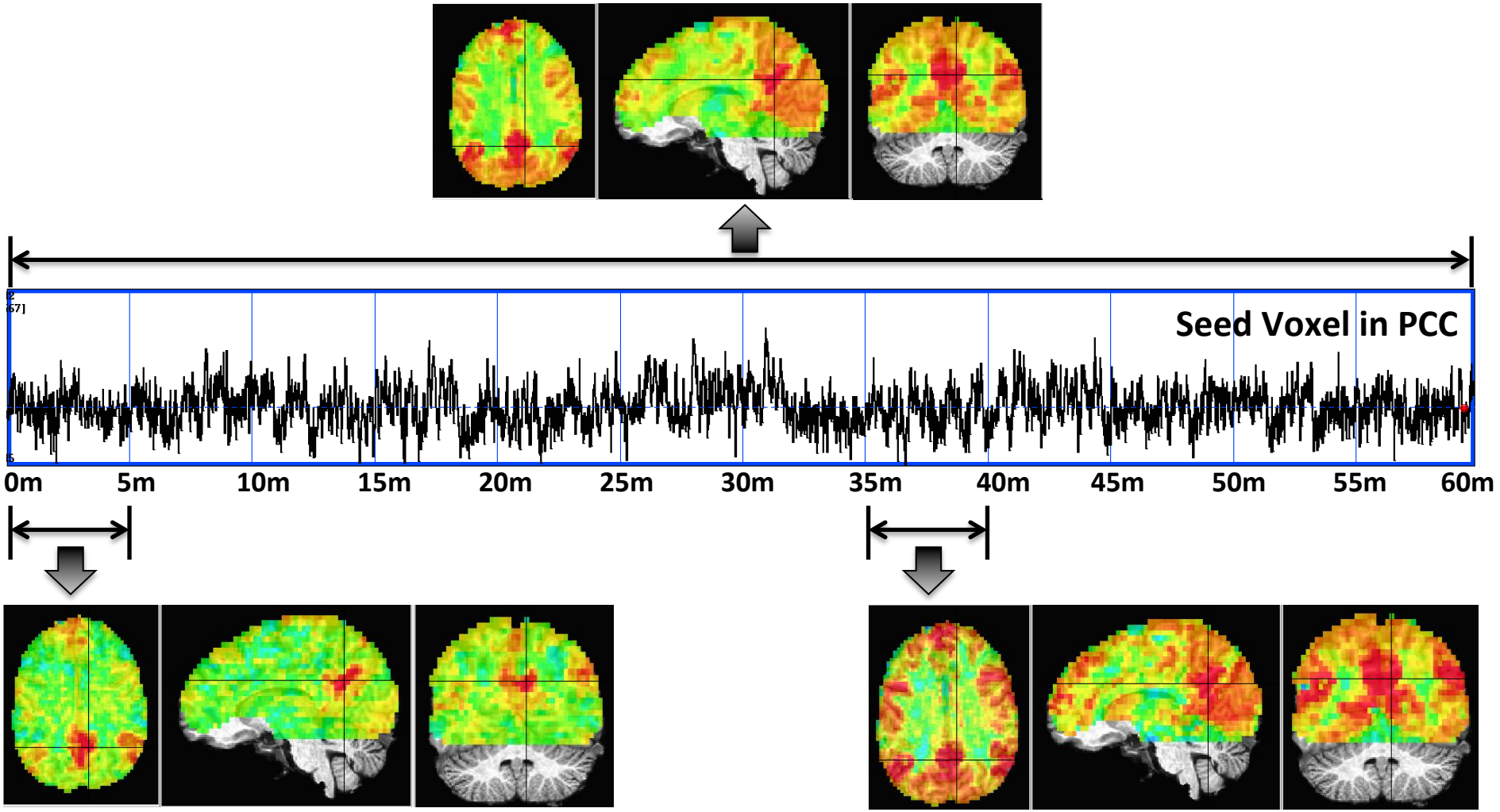


BOLD Connectivity Dynamics: Definition



60 Minutes of Continuous Rest Data | TR = 1s

Agenda

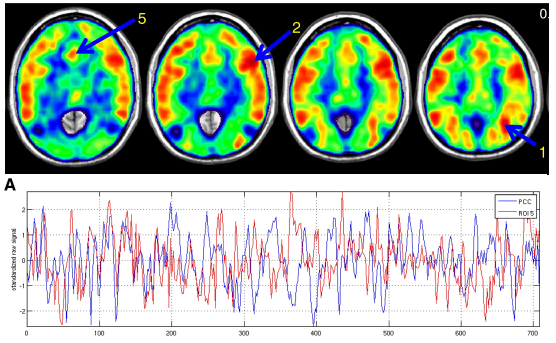
- **BOLD Connectivity Dynamics**
  - Some Original Observations
  - Basic Characterization of this Phenomena

- **Relationship to On-Going Cognition**
  - Automatic sleep staging based on fMRI connectivity
  - Detection of cognitive states using whole brain connectivity patterns

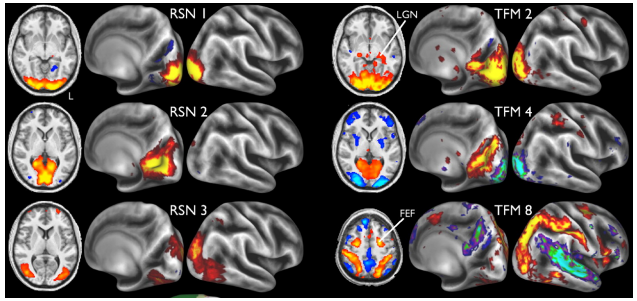
- **Importance of Methodology Decisions**
  - Parcellation Scheme
  - Feature Selection
  - Data mining Algorithm

Intro - Original Observations

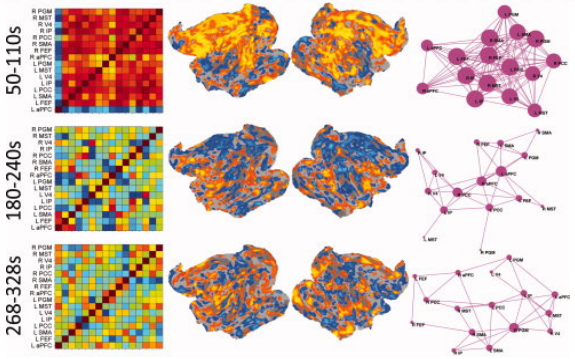
- **Chang & Glover, NeuroImage 2009**
  - Connectivity between PCC and other regions vary significantly across time.
  - This variability is region dependent.
  - Connectivity fluctuates between pos & neg values.



- **Smith et al., PNAS 2009**
  - Identify networks by virtue of temporal independence (TFM).
  - Identified TMFs include several that subdivide the default-mode network into several functionally distinct, spatially overlapping, networks.
  - TFMs are quite different from resting-state networks previously reported, and may have greater biological interpretability.



- **Hutchison et al., Human Brain Mapping 2012**
  - Short term connectivity profiles differ significantly from stationary patterns.
  - Dynamic changes happen also in anesthetized monkeys.



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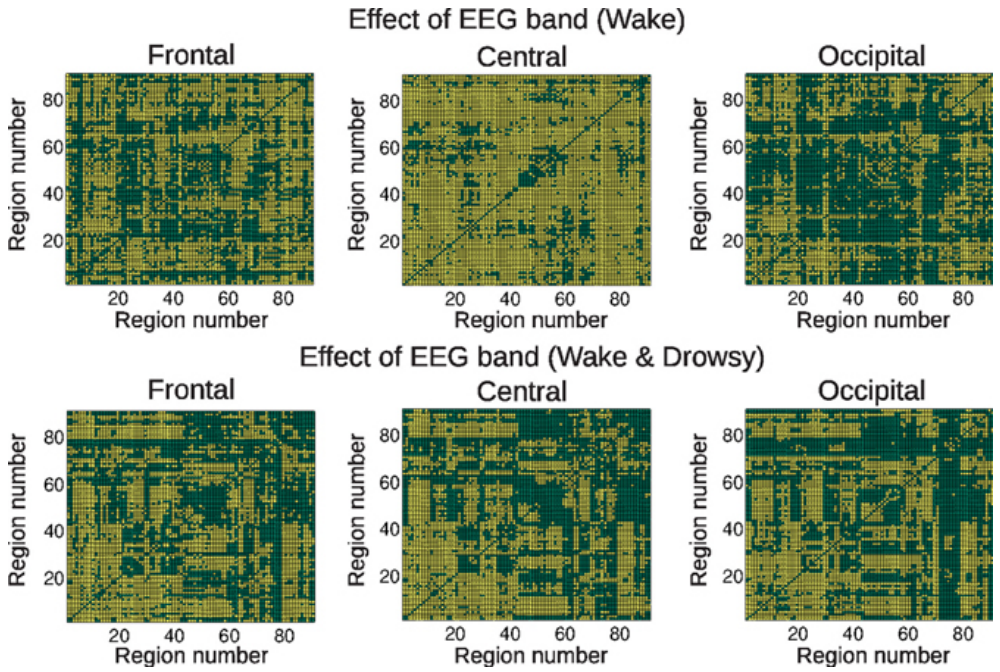
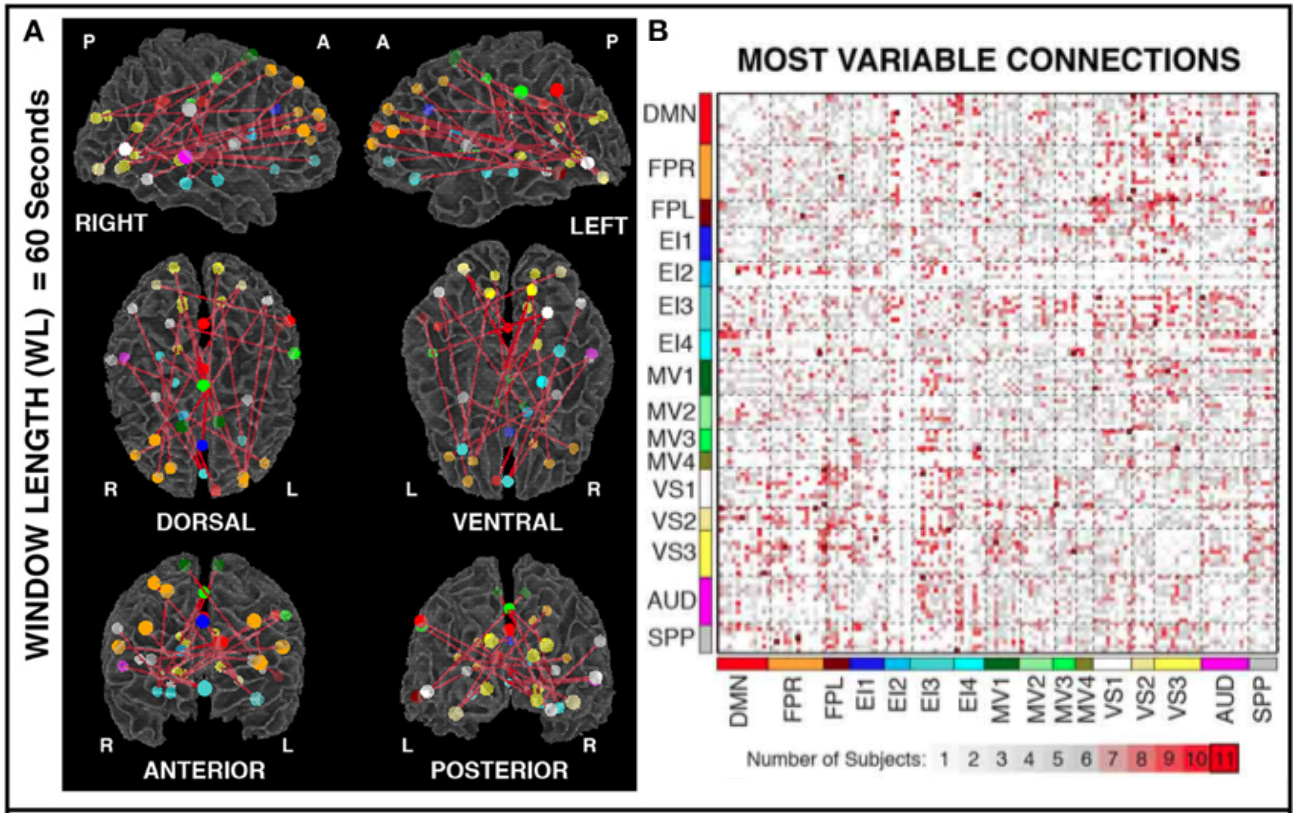
Intro – Correlations with EEG

- **Tagliazzuchi et al. , Front. Human Neuros. 2012**
  - Concurrent EEG and fMRI awake and vigilance changes
  - Increased α (8-12Hz) & β (15-30Hz) power → decrease functional connectivity
  - Gamma power (30 – 60Hz) correlated positively with functional connectivity.
  - Suggest that "fluctuations in BOLD connectivity have a neurophysiological origin".

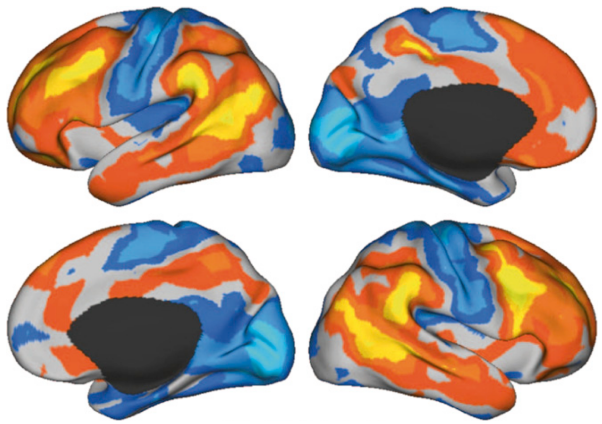


- **Chang et al. , NeuroImage 2013**
  - Also reports correlations between EEG & fMRI connectivity changes at these sort temporal scales.
  - Focus on DMN, Dorsal Attention and Salience Networks

Spatial Distribution of Stability of Connectivity – Most Variable Connections



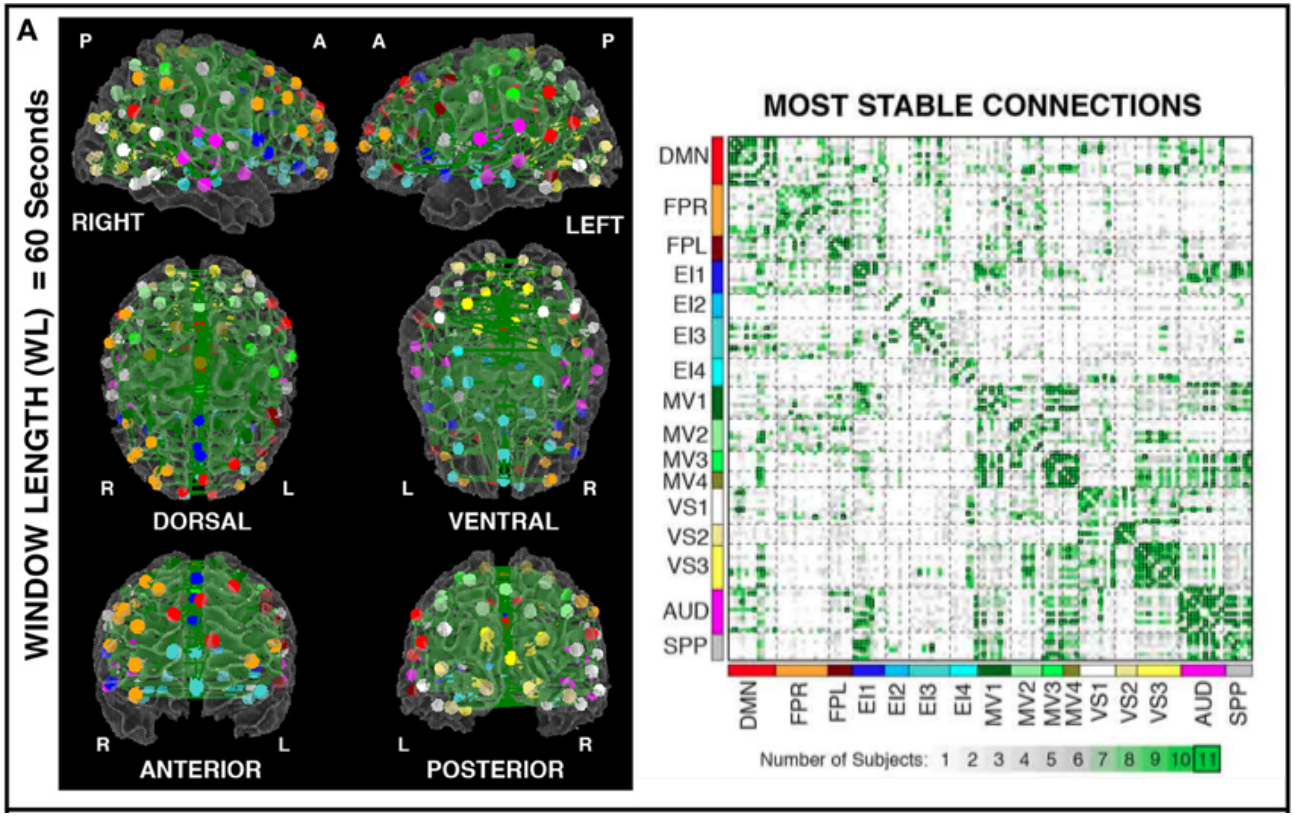
Gonzalez-Castillo et al. 2014 (Frontiers in Neuroscience)

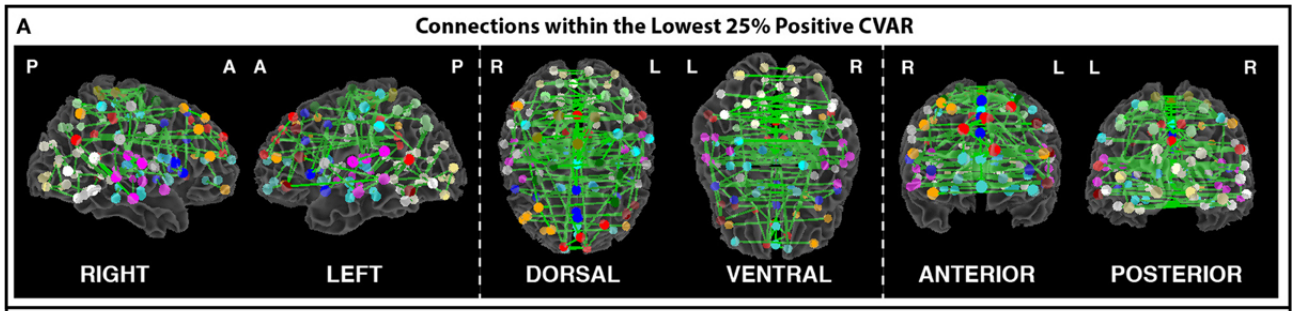


(Mueller et al. 2013)

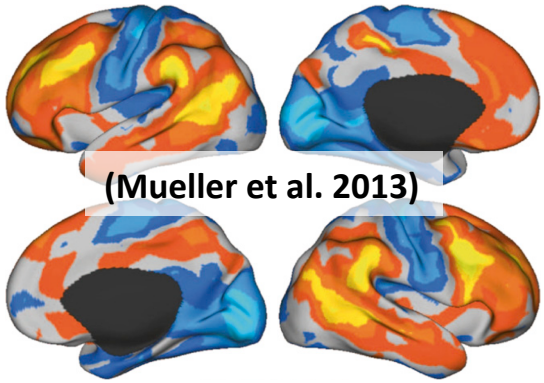
- Primarily inter-network, inter-hemispheric connections involving the fronto-parietal network and occipital regions. Also some DMN regions.
- Sme overlap with:
  - Hetero-modal regions with largest levels of inter-subject variability in stationary patterns of connectivity. (Mueller et al., Neuron 2013)

Spatial Distribution of Stability of Connectivity – Most Stable Connections





- Largest pool of connections.
- Mostly symmetric, inter-hemispheric connections between homologous right/ left regions.
- Only account for 32% of intra-network connections → Networks are flexible
- Unimodal sensory-motor networks (VIS, AUD and MV) seems to be among the most stable.



(Mueller et al. 2013)

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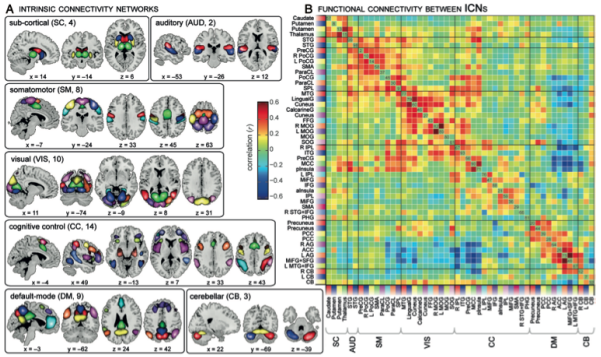
Rest BOLD Dynamics – Functional Connectivity States

- **APPROACH:** Explored resting state data from over 400 subjects with a combination of:

WHOLE-BRAIN CONNECTIVITY



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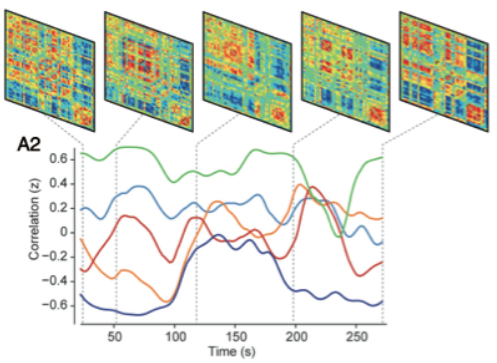
SLIDING WINDOW ANALYSIS



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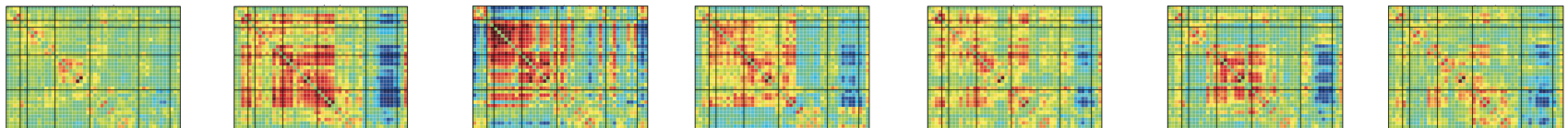
K-MEANS Clustering

- **FINDING:** a series of re-ocurrent short-term (in the order of seconds) whole-brain connectivity patterns that are common across subjects.



Allen et al. "Tracking whole-brain connectivity dynamics in the Resting State" Cer. Cortex 2014

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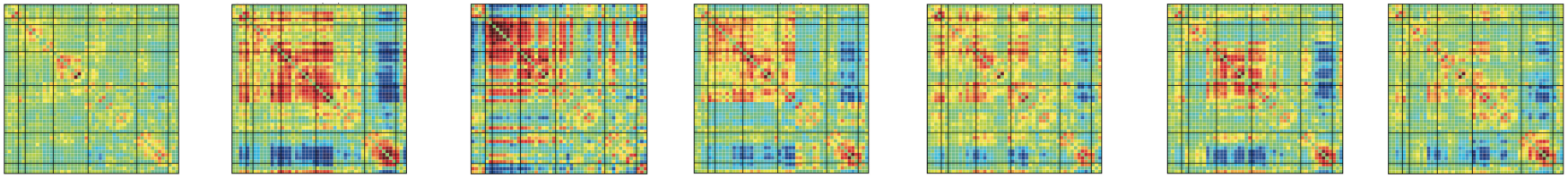
Interim Summary

FUNCTIONAL CONNECTIVITY STATES



FC STATE 1 | FC STATE 2 | FC STATE 3 | FC STATE 4 | FC STATE 5 | FC STATE 6 | FC STATE 7

Allen et al. "Tracking Whole-brain Connectivity Dynam[illegible]the Resting State" Cerebral Cortex (2012)

SUBJECTS AT REST SWITCH BETWEEN COGNITIVE STATES EVERY FEW SECONDS

Mental activity description: occurrence and proportion, the average time spent during the experiment, and the occurrence and proportion of participants showing a dominance. IMAG: visual mental imagery; LANG: inner language; SOMA: somatosensory awareness; MUSI: inner musical experience; NUMB: mental processing of numbers.

Mental activity	Number of participants reporting the activity (% of 180)	Average time spent in the reported activity[a] %[2] ± SD	Number of participants reporting at least 50%[b] of the mental activity (%)
IMAG	171 (95)	40 ± 22	63 (35)
LANG	167 (93)	30 ± 19	31 (17)
SOMA	170 (94)	19 ± 16	12 (7)
MUSI	92 (51)	23 ± 17	11 (6)
NUMB	62 (34)	12 ± 10	1 (<1)

Delamillieure et al. "The Resting State Questionnaire: an introspective questionnaire for evaluation…". Brain Res Bull. (2011)

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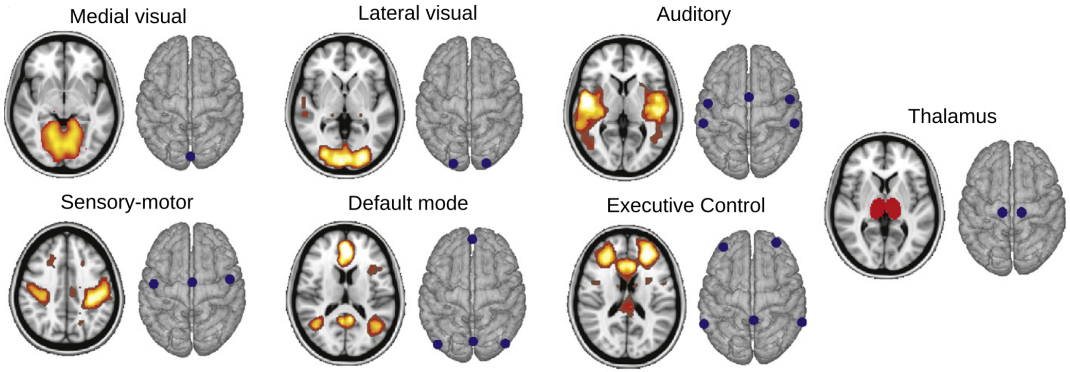
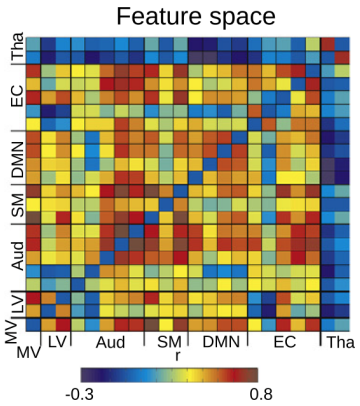
FC & Cognition – Dynamics (I) – Sleep Stages

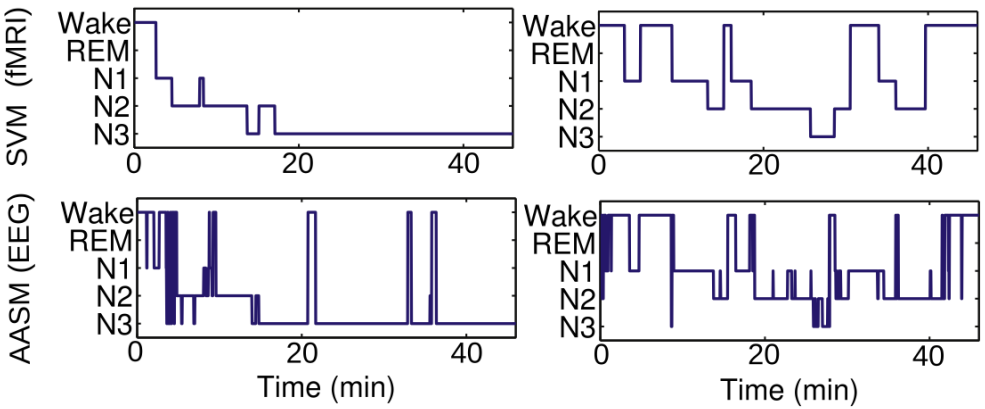
- **Feature Space**: connectivity between 22 ROI selected based on prior studies of sleep.

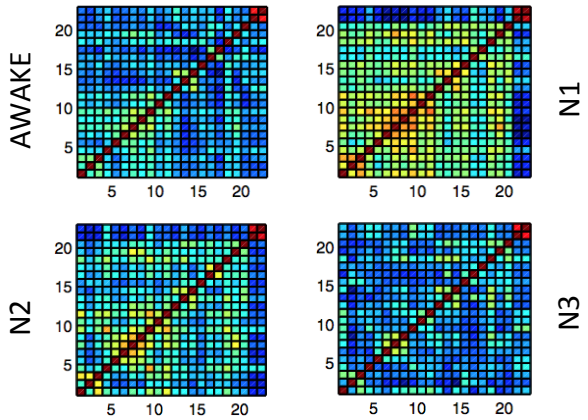




- **Temporal Scale**: 4 min – 1 min sliding windows across a 52m scan

- **Results:**
  - Accuracy > 80% (Agreement between fMRI-based and EEG-based staging)
  - For epochs as short as 60s



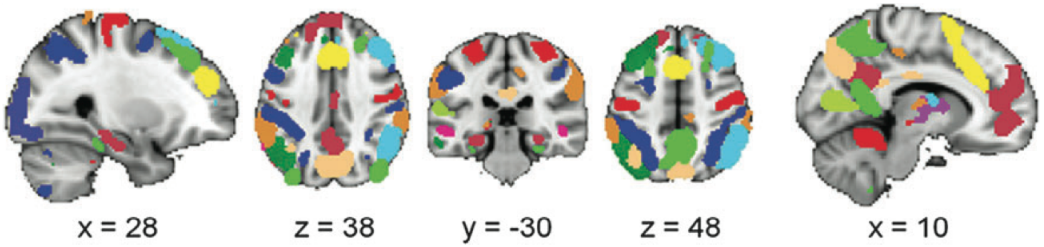


Tagliazzuchi et al. "Automatic sleep staging using fMRI connectivity data". NeuroImage 2012

FC & Cognition – Dynamics (II) – Differentiate Known Cognitive states

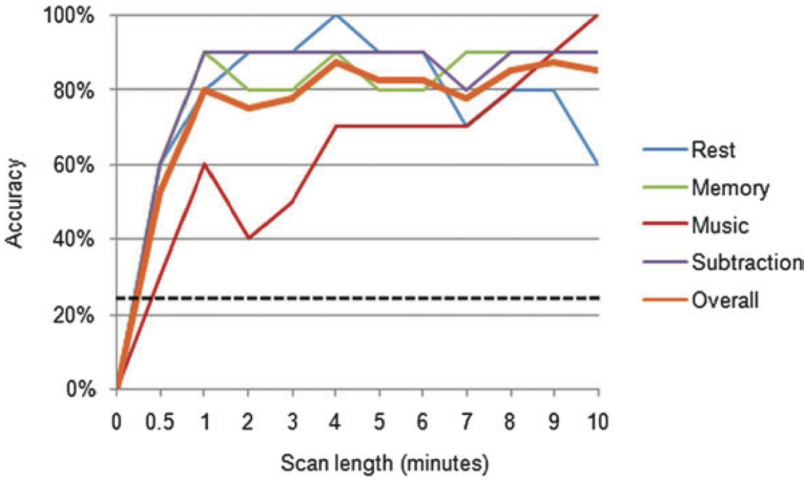
Objective: Attempt decoding of cognitive states on the basis of whole-brain connectivity computed over short periods of time using a classifier (supervised classification).

- **Feature Space:** subset of ROIs with significantly different connectivity across the states selected from a 90 ROIs covering the majority of Gray Matter



- **Data**:
  - 10 min scans during which subjects were always on the same "state"
  - States: rest, episodic memory, numerical subtraction, silent singing.

- **Results:**
  - ~ 84% Accuracy for whole scans
  - ~80% Accuracy for 60s windows
  - Large drop in accuracy for shorter windows



Shirer et al. "Decoding cognitive states with whole-brain connectivity patterns" Cer. Cortex 2012

FC Dynamics & Cognition – Interim Summary

WHAT WE KNOW ALREADY

- During rest one can observe short term (several seconds long) re-occurring patterns of whole brain connectivity that are common across subjects. **[Allen et al. 2014]**
- Case-specific connectivity patterns associated with short time windows (45 – 60s) can be used to reliably differentiate sleep stages **[Taggliazzuchi et al., 2012]** and cognitive states **[Shirer et al., 2012]** using supervised classification methods.

DYNAMIC CHANGES IN REGION-SPECIFIC FUNCTIONAL CONNECTIVITY PATTERNS SEEM TO BE STRONGLY RELATED TO ON-GOING COGNITION

LIMITATIONS OF THESE STUDIES

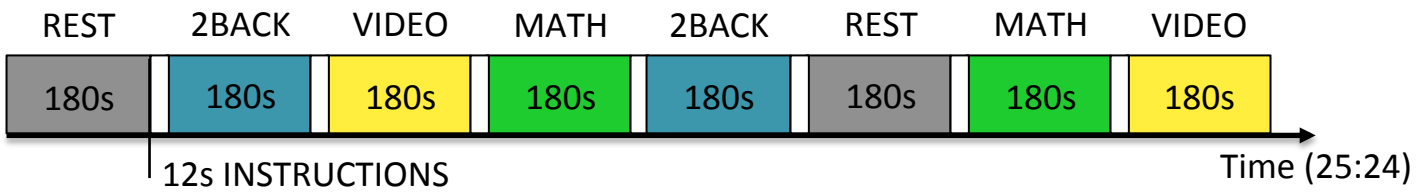
- **[Taggliazzuchi et al.] & [Shirer et al.]**
  - Informed selection of ROIs based on target states
  - Supervised Classification Approach that needs training dataset & labels.
- **[Allen et al.]** → Interpretational Challenge

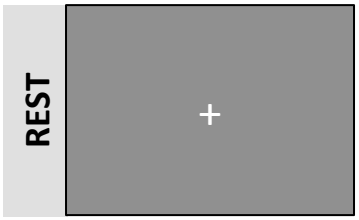
OPEN QUESTIONS

Can we robustly detect on-going "COGNITIVE STATES" on the basis of whole-brain "FC STATES" using completely unsupervised methods at the single-subject level?

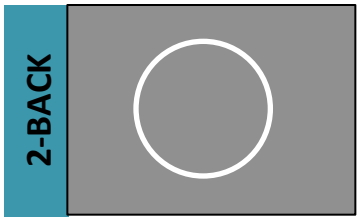
How robust is this FC STATE ←→ COGNITIVE STATE relationship against analytical/ methodological decisions (e.g., atlas, feature selection scheme, temporal scale, etc.)?

METHODS - Experimental Design

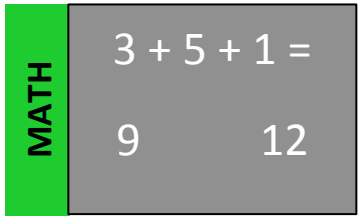




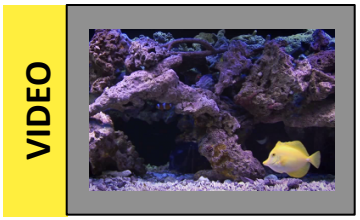
Passively stare at the crosshair in the center of the screen.



Press button when the shape on screen is the same as two before.



Select the correct answer from the two available options.



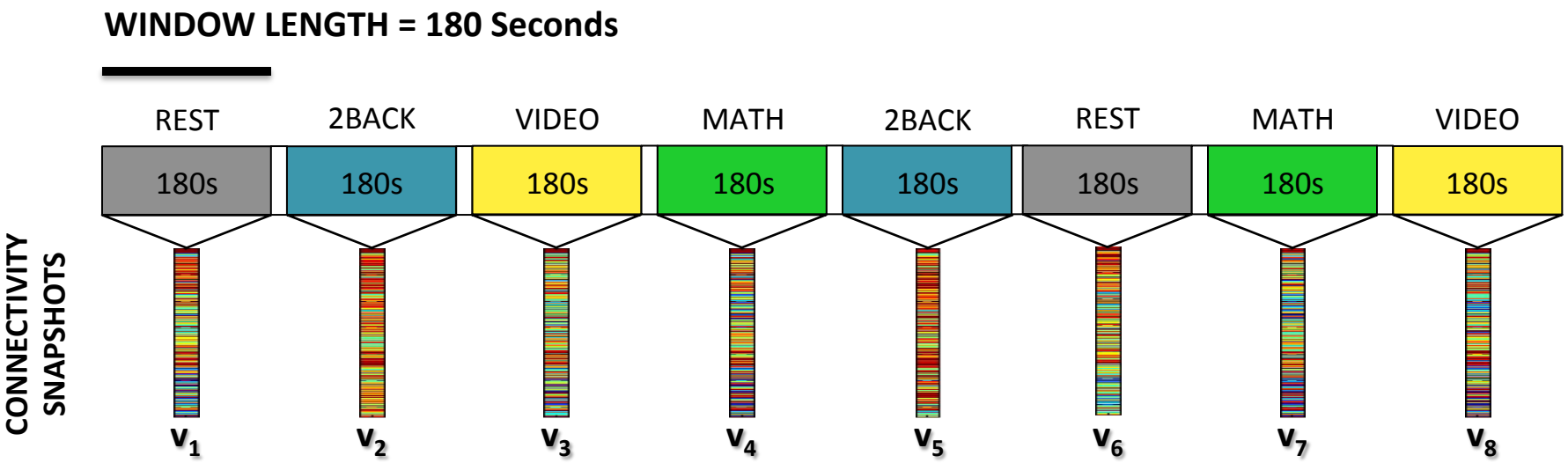
Identify the type of fish when a crosshair appears on a target fish (clown or other type).

1. DATA COLLECTION

- 22 Subjects
- 7T Siemens | 32 Ch Coil
- MP-RAGE 1mm^3
- Proton Density 1mm^3
- GRE-EPI
  - TR/TE = 1.5s/25ms
  - Resolution = 2mm^3
  - #Acquisitions = 1017
  - Full Cerebrum Coverage | No Cerebellum

METHODS - Data Analysis

PREPROCESSING	TS EXTRACTION	DIMENSIONALITY REDUCTION	**SLIDING WINDOW CONNECTIVITY**	CLUSTERING



METHODS - Data Analysis

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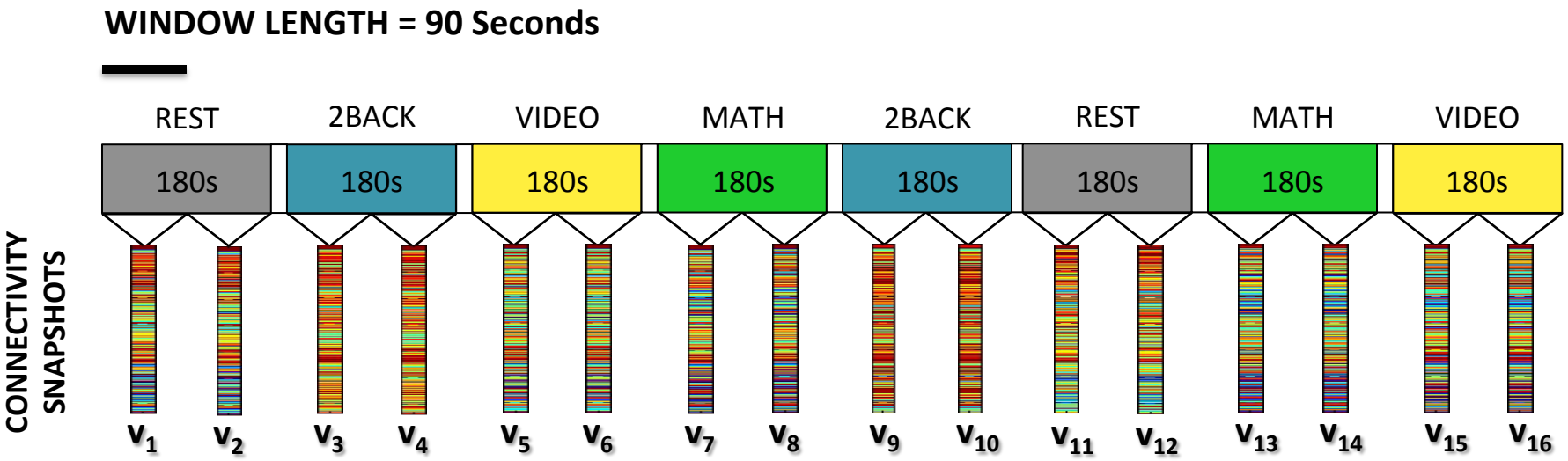
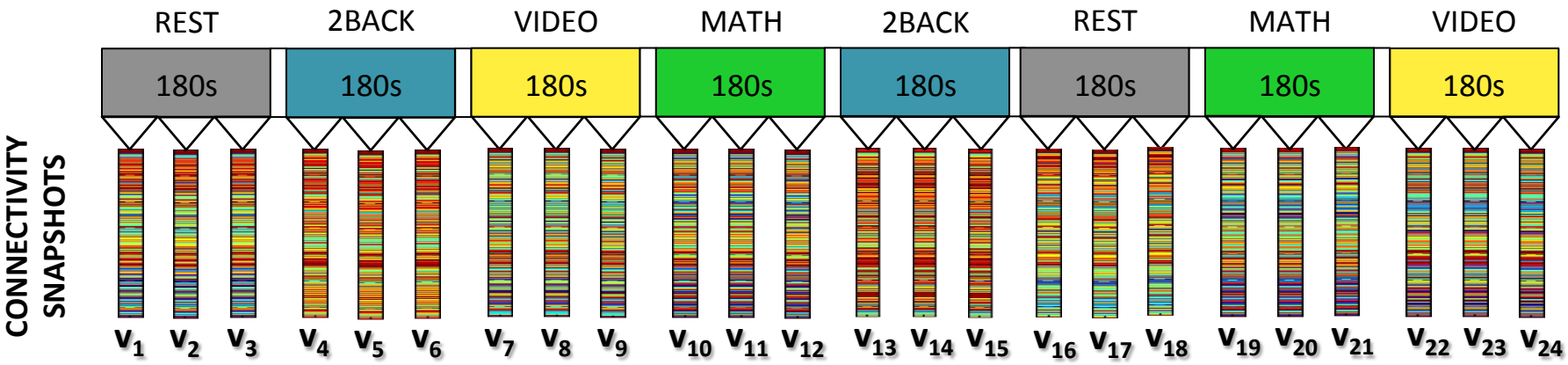


METHODS - Data Analysis

PREPROCESSING	TS EXTRACTION	DIMENSIONALITY REDUCTION	**SLIDING WINDOW CONNECTIVITY**	CLUSTERING

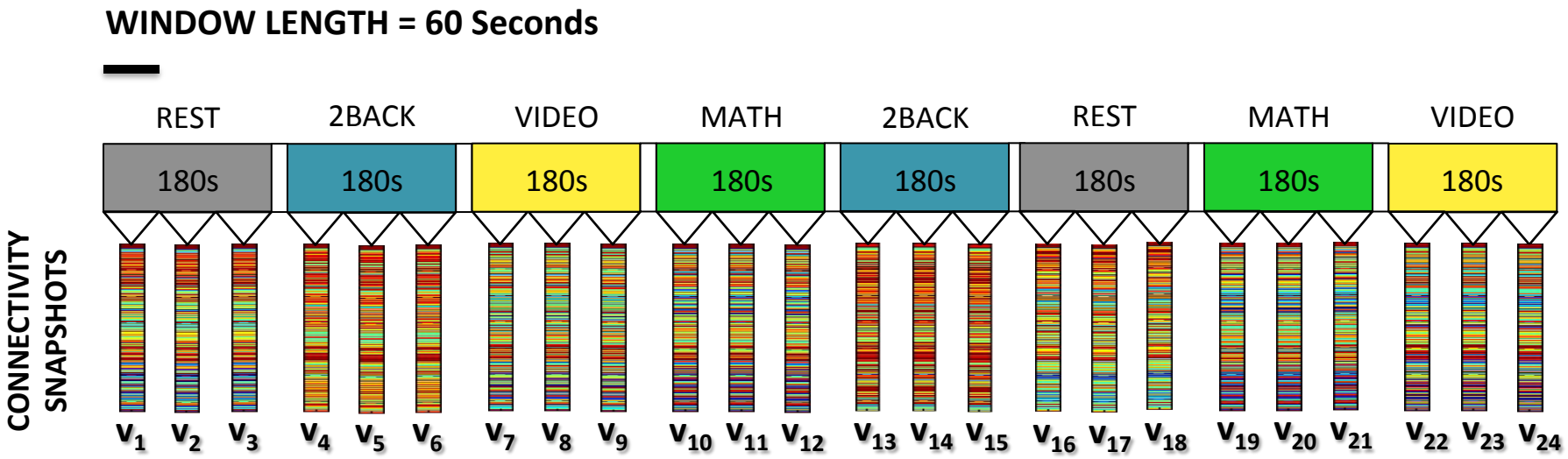
WINDOW LENGTH = 60 Seconds



WINDOW LENGTH	180s	90s	60s	45s	30s	15s
# Windows	8	16	24	32	48	96
# TRs in Window	120	60	40	30	20	10

METHODS - Data Analysis

PREPROCESSING	TS EXTRACTION	DIMENSIONALITY REDUCTION	SLIDING WINDOW CONNECTIVITY	**CLUSTERING**



METHODS - Data Analysis

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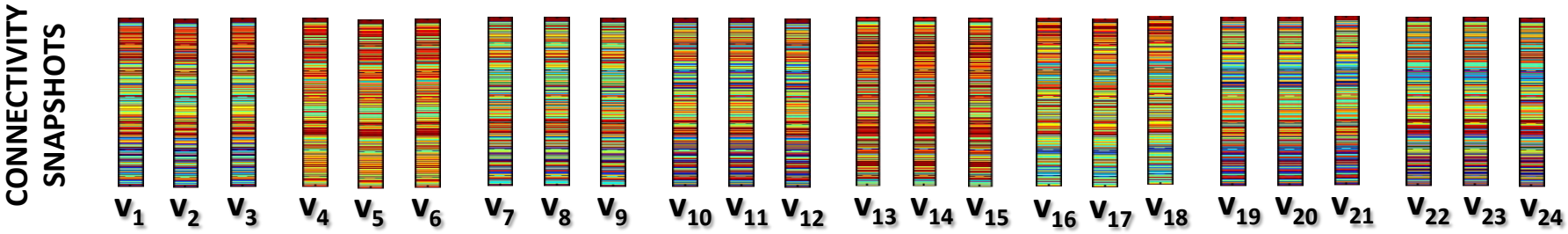
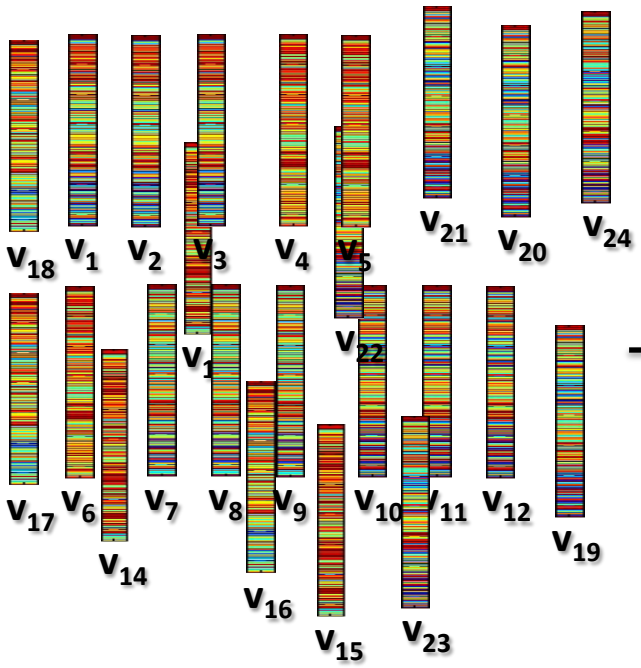
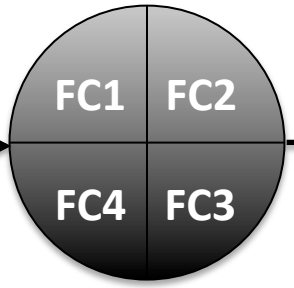
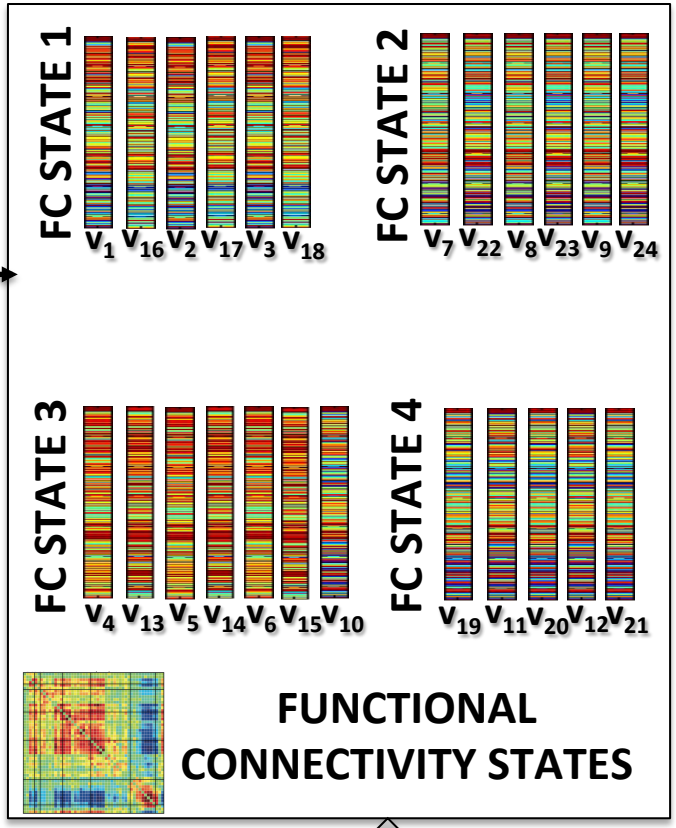


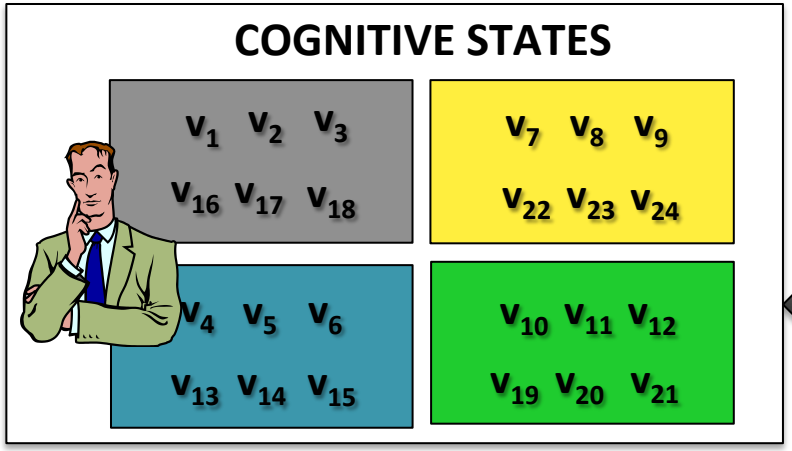
METHODS - Data Analysis

PREPROCESSING | TS EXTRACTION | DIMENSIONALITY REDUCTION | SLIDING WINDOW CONNECTIVITY | **CLUSTERING**



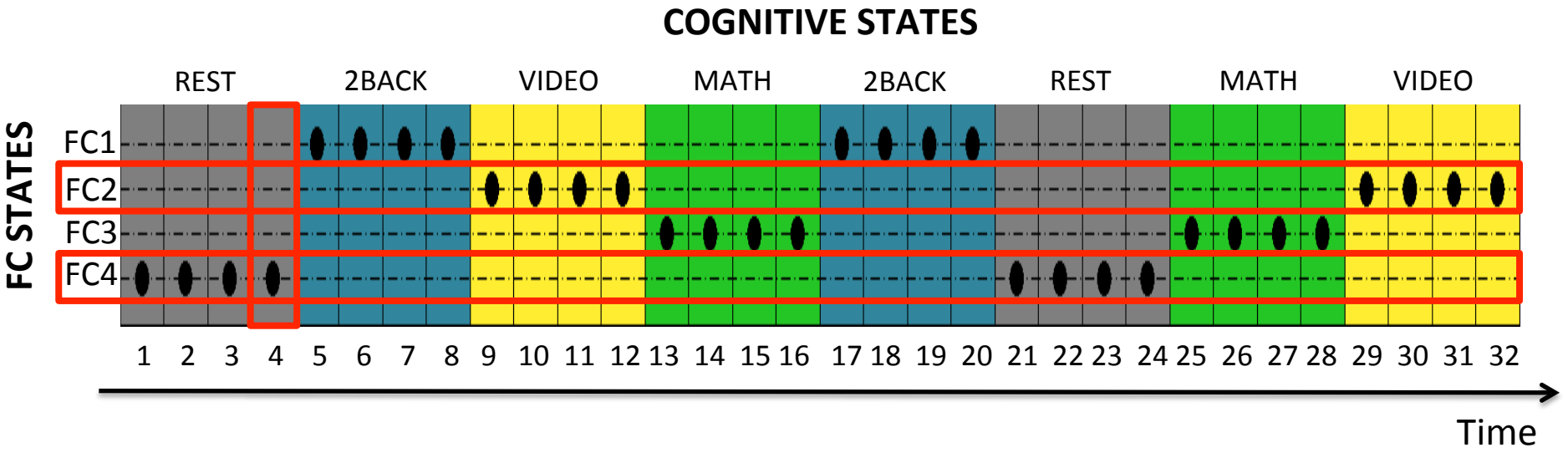






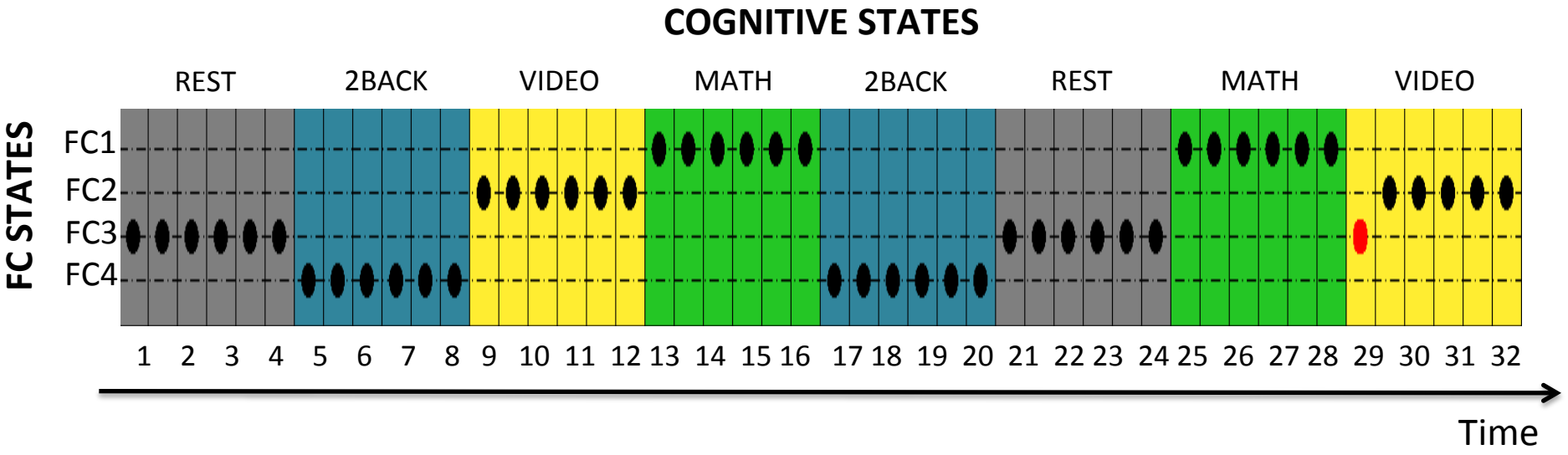
CLUSTER VALIDATION

METHODS – Visual Validation



Window Length = 45s | 32 Windows

METHODS – Visual Validation



Window Length = 30s | 48 Windows

METHODS – Quantitative Validation

EXTERNAL MEASURE OF CLUSTERING VALIDATION

Evaluate the level of agreement between a given partition (k-means output | FC STATES) and an external "true" classification (experimental paradigm | COGNITIVE STATES)

METRIC: ADJUSTED RAND INDEX (ARI)

$$\frac{\text{Number of Pairs in Agreement}}{\text{Total Number of Pairs}}\ *$$

* Corrected for random agreement between two random partitions

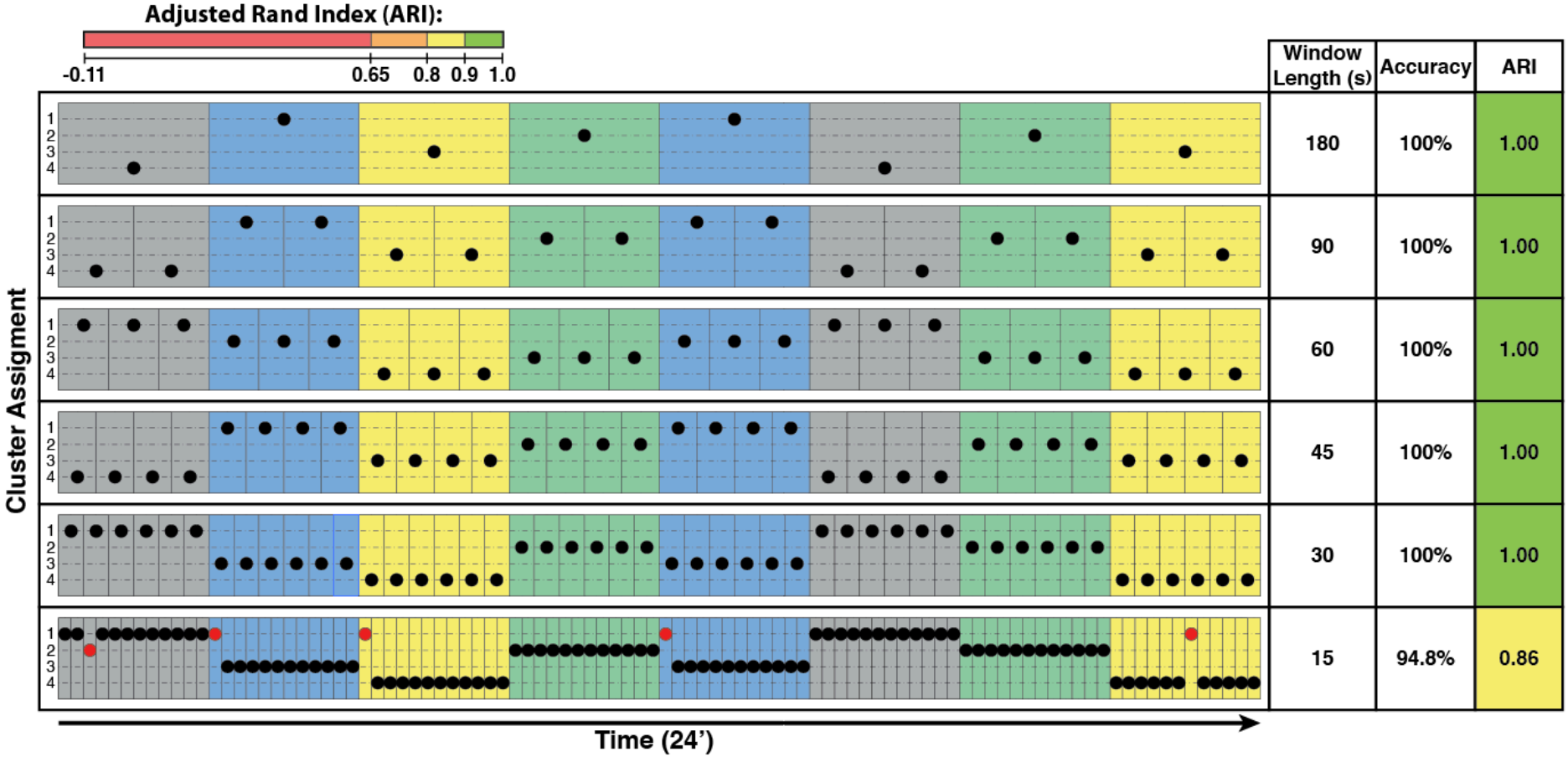
Hubert L. et Arabie P. "Comparing Partitions". Journal of Classification: 2, 193-218 (1985)

INTERPRETATION CRITERIA

[-0.11, 0.65] → Poor Recovery
[0.65, 0.80] → Moderate Recovery
[0.80, 0.90] → Good Recovery
[0.90, 1.00] → Excellent Recovery

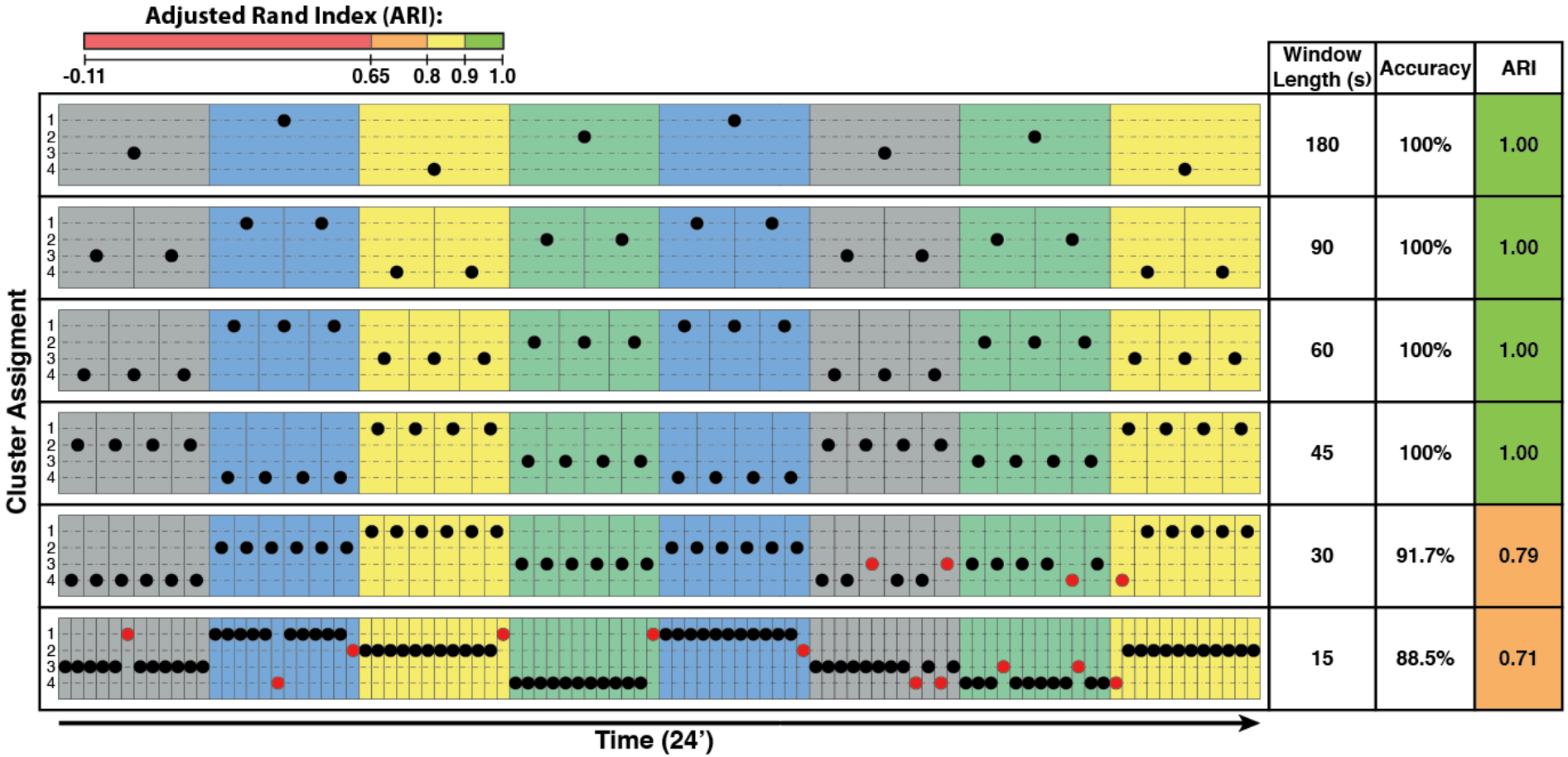
Steinley D. "Properties of the Hubert-Arabie Adjusted Rand Index". Psy Methods:9 (3), 386-396 (2004)

RESULTS – Excellent Subject



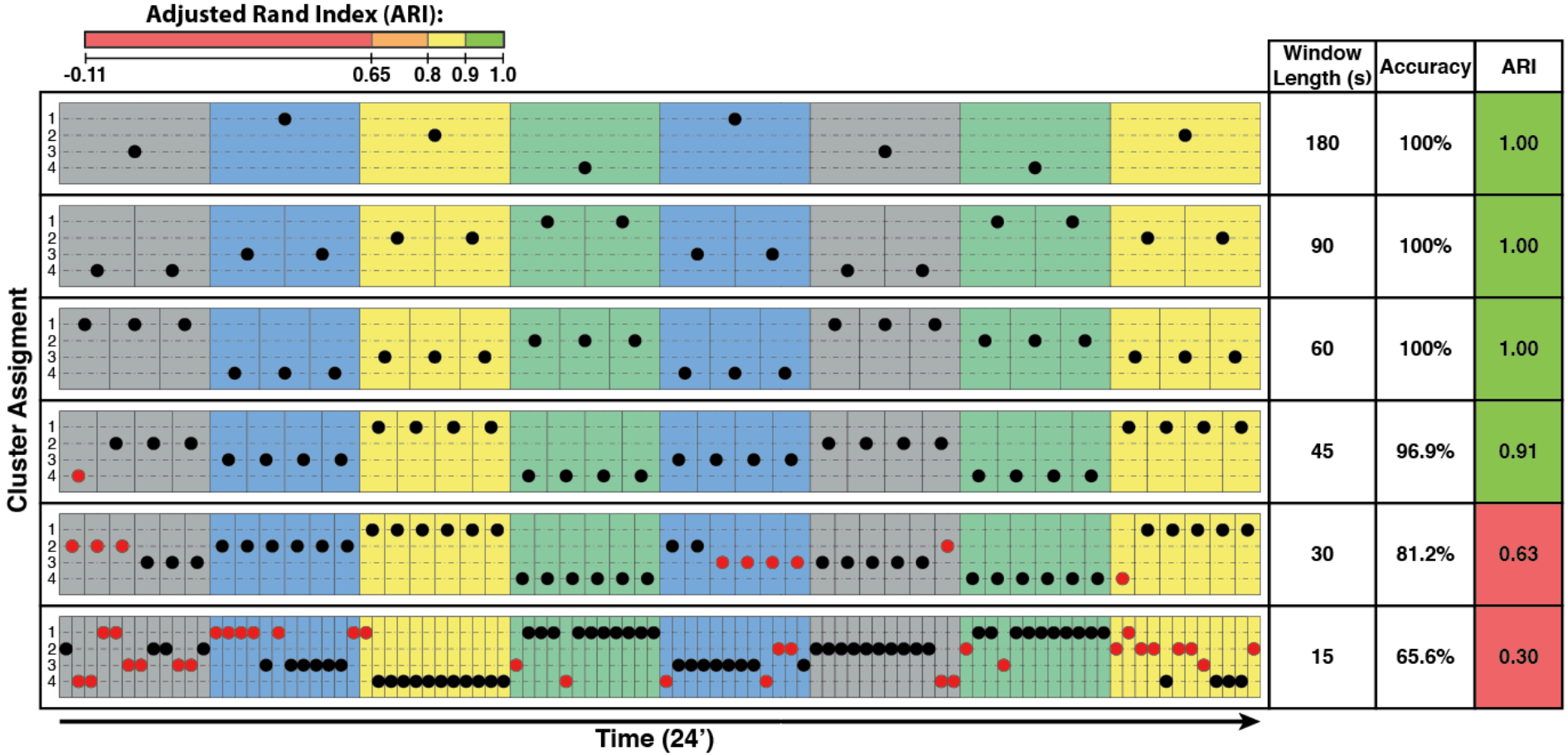
Window Length (s)	Accuracy	ARI
180	100%	1.00
90	100%	1.00
60	100%	1.00
45	100%	1.00
30	100%	1.00
15	94.8%	0.86

RESULTS – Moderate Subject



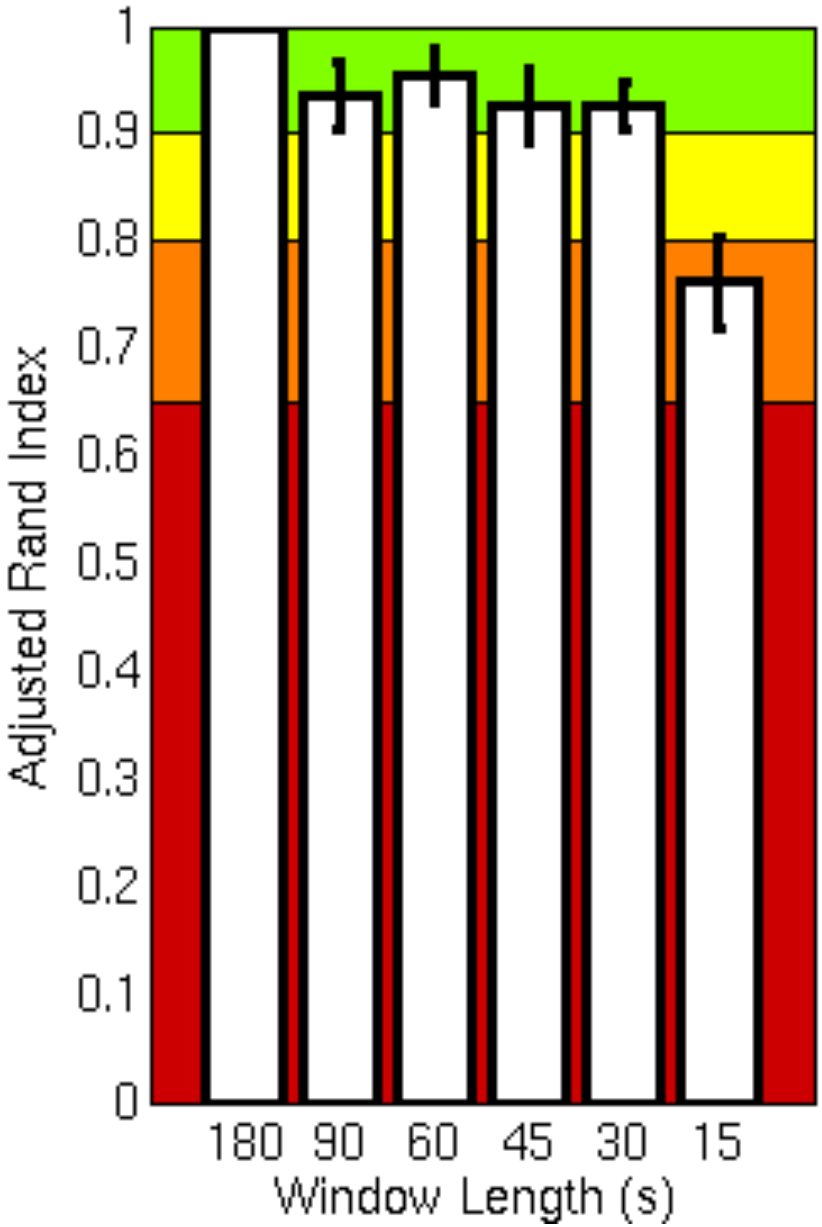
Window Length (s)	Accuracy	ARI
180	100%	1.00
90	100%	1.00
60	100%	1.00
45	100%	1.00
30	91.7%	0.79
15	88.5%	0.71

RESULTS – Poor Subject



Window Length (s)	Accuracy	ARI
180	100%	1.00
90	100%	1.00
60	100%	1.00
45	96.9%	0.91
30	81.2%	0.63
15	65.6%	0.30

Results – Classification Accuracy



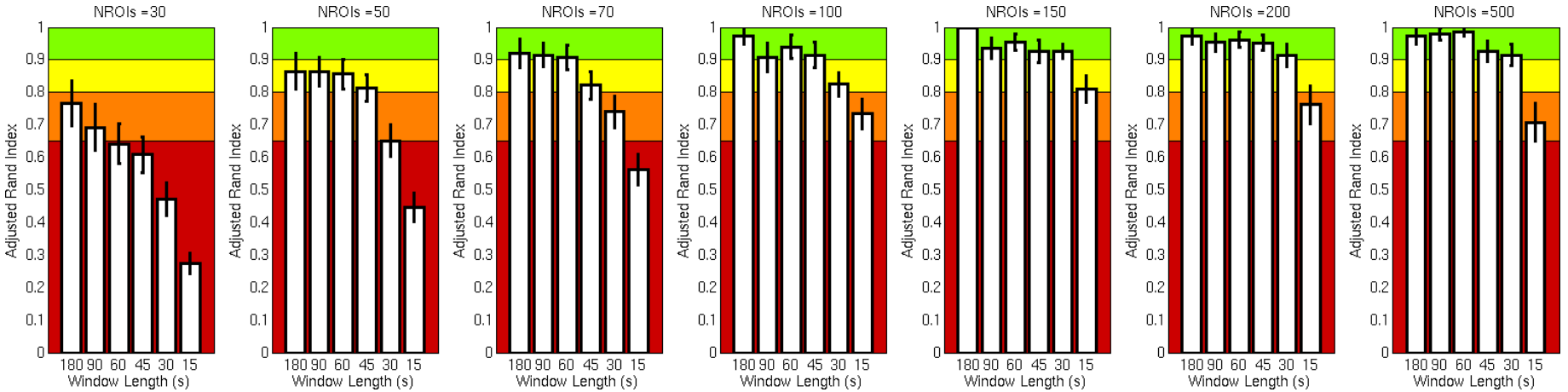
Group Classification Accuracy

Agenda

- **BOLD Connectivity Dynamics**
  - Some Original Observations
  - Basic Characterization of this Phenomena
- **Relationship to On-Going Cognition**
  - Automatic sleep staging based on fMRI connectivity
  - Detection of cognitive states using whole brain connectivity patterns
- **Importance of Methodology Decisions**
  - Parcellation Scheme
  - Feature Selection
  - Data mining Algorithm

Methodology Matters? – Brain Parcellation

PRE-PROCESSING	**PARCELLATION**	GENERATE ROI-TS	DIMENSION REDUCTION	CONNECTIVITY	CLUSTERING



30 ROIs | 50 ROIs | 70 ROIs | 100 ROIs | **150 ROIs** | 200 ROIs | 500 ROIs

More smaller ROIs (more detailed connectivity patterns) seem to be preferable up to around 150 – 200. Beyond that there is no real gain, perhaps due to the increased dimensionality

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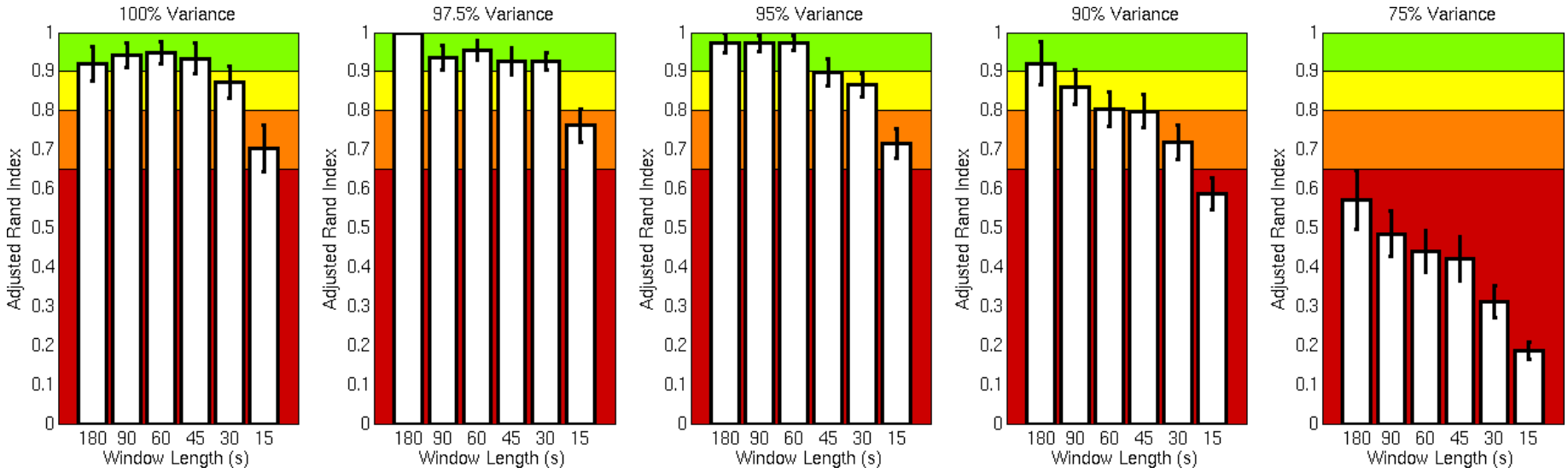
Methodology Matters – How much variance to keep?

PRE-PROCESSING | PARCELLATION | GENERATE ROI-TS | **DIMENSION REDUCTION** | CONNECTIVITY | CLUSTERING

150 ROIs Atlas



100%	97.5%	95%	90%	75%
(130)	(61)	(42)	(25)	(9)

Dimensionality Reduction (Feature Selection) greatly improves partition results.
Excessive Dimensionality Reduction can be damaging as well.

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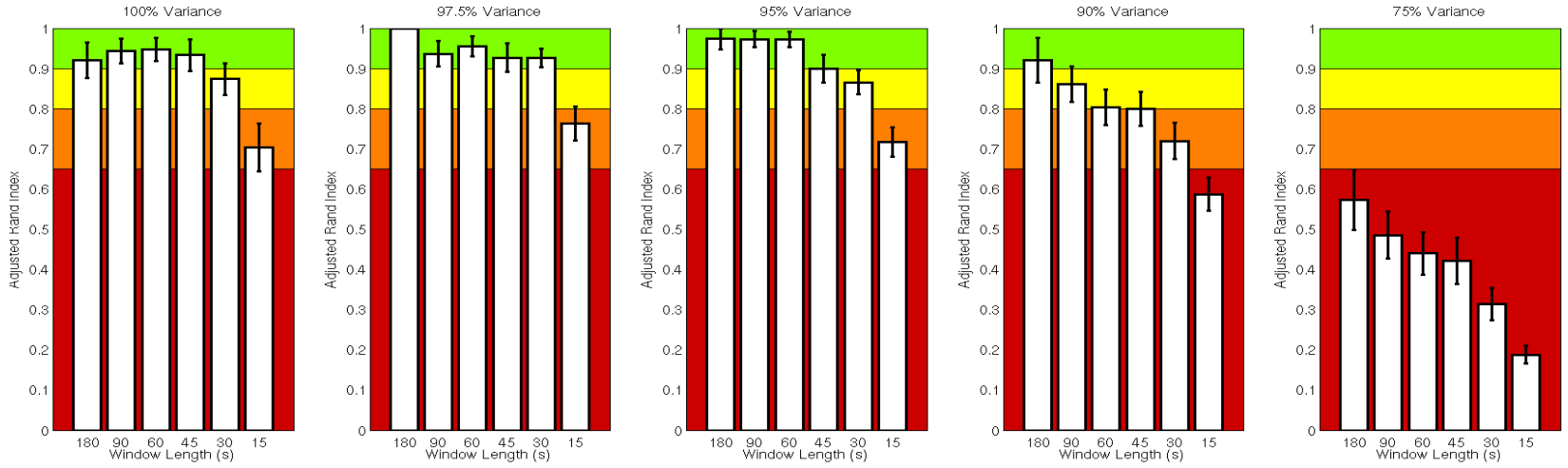
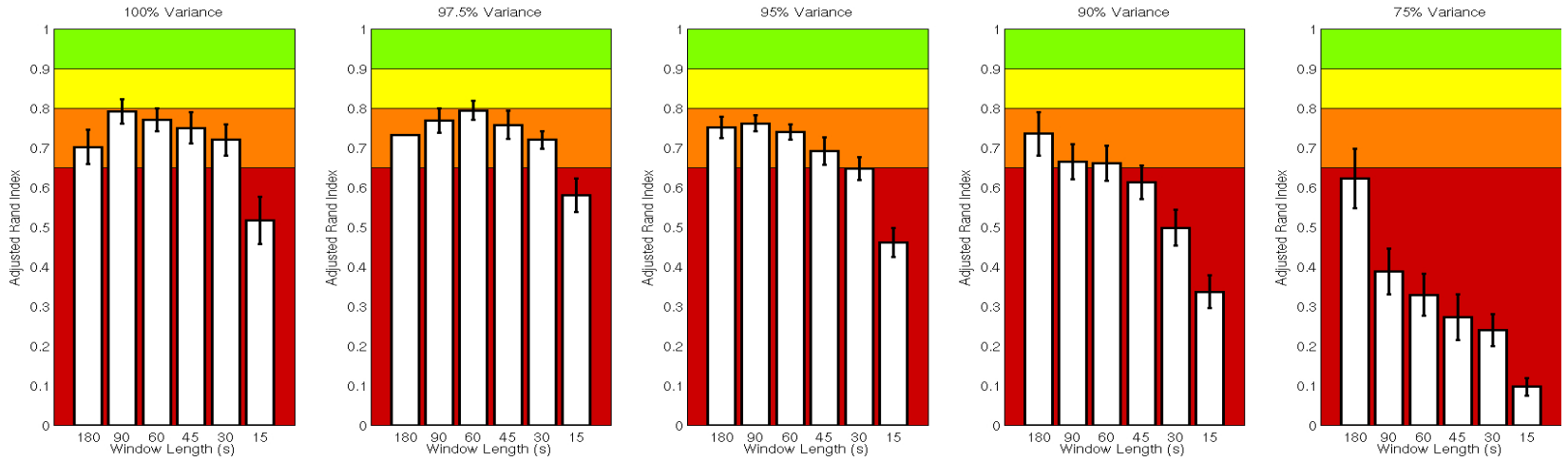
Methodology Matters – Clustering Technique?

PRE-PROCESSING	PARCELLATION	GENERATE ROI-TS	DIMENSION REDUCTION	CONNECTIVITY	**CLUSTERING**

K-MEANS



HIERARCHICAL CLUSTERING



K-Means outperforms Hierarchical Clustering

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Conclusions (I)

- Despite long-term stability of resting-state networks, these networks are quite dynamic at shorter temporal scales:
  - Dynamic patterns can significantly differ from "stationary patterns"
  - Dynamic behavior is region dependent
  - Present both in awake and anesthetized subjects.
- Whole-brain short-term (tens of seconds) fMRI-based connectivity patterns can be used as a marker to successfully recover different cognitive states.
  - Dynamic changes in connectivity are strongly related to on-going cognition.
  - Good classification can be achieved with epochs as short as 15 – 60 seconds.
- Methodological decisions can affect the strength of the relationship between dynamic connectivity changes and on-going cognition.

Conclusions

- Measures of Connectivity Dynamics may be clinically relevant
  - Differences in dynamic FC between healthy control and minimally disabled relapse-remitting multiple sclerosis patients.
  - Identified a network of connections centered on the default-mode network with altered contribution in patients.

[Leonardi et al., NeuroImage 2013]

- We need to better understand the phenomena/contributing factors
  - What are the periods of hyper-connectivity (simply deep breathing?)
  - Should this dynamic behavior affect the way we define/design resting state studies? What about longitudinal studies?

- Necessary Methodological Developments:
  - Automatically obtain number of states from the data
  - Automatically detect transitions
  - Find optimal ways to compress the data, yet keep all informative bits (e.g., graph theory metrics)

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